missing completely at random assumption was indeed violated, and the pattern they observed may not have been even missing at random, since the missing pattern may depend on the outcome that is not available from the dropouts. If this is the case, then the pattern of missing data is informative, and as we mentioned in our editorial, using pattern-mixture models may be appropriate. Subjects are first divided into groups based on their missing data patterns and parameters estimated, and then results are aggregated. Although this approach is intuitively attractive, it can be difficult to apply in practice, since it is necessary to have adequate numbers with each pattern to adequately apply this methodology. Further, the data may lack power to detect the extent to which the missing assumption arises informatively, hence the need for other approaches, such as shared parameter models and definitely sensitivity analysis.

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Drs. Damaraju, Olson, and Canuso Reply

TO THE EDITOR: We appreciate the insightful comments made by Drs. Potkin and Siu in their reference to our article. As the editorial accompanying our article observed, the proportion of missing data in our study was small (<20%). The likelihood-based mixed-model repeated-measures analysis is generally robust to departures from the missing at random assumption when the sample size is large and the number of dropouts is small (1). In our study, results were consistent between the last observation carried forward and mixed-model repeated-measures analyses of the primary efficacy endpoint (day 14) based on the intent-to-treat data set. The mixed-model repeated-measures analyses utilized PANSS score data obtained at all visits, including the dropout visit.

Missing data arise under different conditions. Missing completely at random means that the observed data are observed at random and the missing data are missing at random, whereas missing at random means only that the missing data are missing at random (2). It is not possible to test the missing at random assumption, since by definition it involves data we do not have (i.e., the missing data). However, it is possible to examine whether the data are consistent with the missing completely at random assumption because the definition of missing completely at random involves observed data, and, in particular, we can examine whether the observed data are observed at random. Although dropout plots are helpful, these could be misleading in instances in which few dropouts occur. We have tested the missing completely at random assumption based on the dropouts during the monotherapy period using a nonparametric method suggested by Diggle et al. (3, 4). We do not find evidence to reject the null hypothesis of completely random dropouts during the monotherapy treatment period in this study (p=0.52).

In general, the mixed-model repeated-measures models are better suited than last observation carried forward models to handle longitudinal data in the presence of dropouts commonly arising in psychiatric clinical trials in which the missing at random assumption appears reasonably plausible. However, we do acknowledge that missing data in psychiatric clinical trials pose serious threats to valid statistical inference when such data are not missing at random. Because the validity of the missing at random assumption cannot be assessed from the data, a sensible approach to inference is to perform sensitivity analyses that account for varying degrees of selection bias (5).

Finally, we thank Drs. Potkin, Sui, and Hamer for their thoughtful comments and the *Journal* for providing the forum to share this discussion. We hope that such exchanges will help researchers as they explore methodologies to best interpret the complexities of clinical trial data.

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Perinatal Akathisia: Implications for Pharmacokinetic Changes During Pregnancy

TO THE EDITOR: Although physiological changes during pregnancy significantly affect drug pharmacokinetics, no evidence-based heuristic exists for peripartum dosing (1). To illustrate this concept, we present the case of a patient with Tourette's syndrome who experienced severe postpartum akathisia, ameliorated by medication dose reduction.

"Ms. HP" was a 29-year-old 3-weeks-postpartum Indian female (gravida 2 para 2), who presented with acute anxiety to the emergency room. Although she had experienced vocal and motor tics since childhood, she had never been treated for these symptoms. Her symptoms became more severe during her second pregnancy. Self-inflicted hitting and face scratching led to a detached retina in the second month of this pregnancy. During the fifth gestational month, her obstetrician started her on pimozide, 4 mg daily. She then reported a prompt and marked reduction in her symptoms, stating that the tics were "almost